1,3-Dipolar Cycloadditions of Some Nitrilimines and Nitrile Oxides to 3-*N,N*-Dimethylamino-1-oxopropene Derivatives

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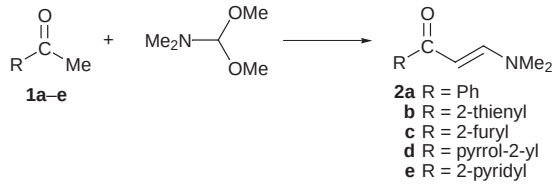
Khadijah Mohamed Al-Zaydi and Ebtisam Abdel Aziz Hafez*

Department of Chemistry, Girls College of Education, Jeddah, P.O. Box 50918 Jeddah 21533, Kingdom of Saudi Arabia

An efficient synthesis of some novel pyrazoles **8a–j**, **13a–e**, **18a,b**, isoxazoles **26a–g**, pyrazolo[3,4-*d*]pyridazines **9a–d** and isoxazolo[3,4-*d*]pyridazines **27a–d** *via* 1,3-dipolar cycloaddition reactions is reported.

Enaminones constitute an interesting class of compounds that are versatile for the synthesis of heterocyclic or aromatic compounds[1,2] and their structural features are found in anticonvulsive[3] and histaminergic compounds.[4]

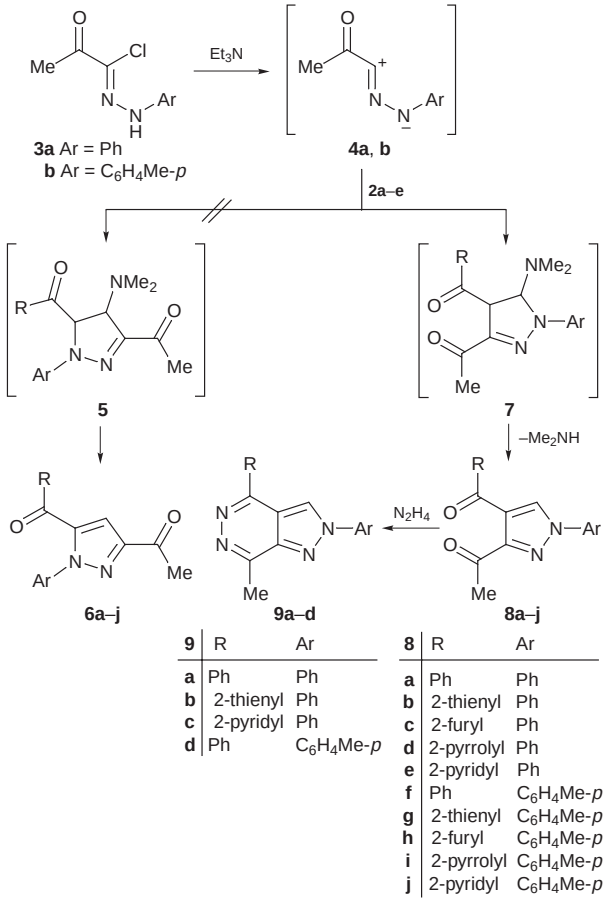
In spite of the enormous amount of literature on the utility of enaminones in heterocyclic synthesis,[5–13] little attention has been paid to their utility as dienophiles in 1,3-dipolar cycloaddition reactions.[14] In continuation of our previous interest in the synthesis of variety of heterocycles from the readily available starting materials for biological screening,[15–17] we report here on the 1,3-dipolar cycloadditions of some nitrilimines and some nitrile oxides to 3-*N,N*-dimethylamino-1-oxopropenes **2a–e**,[18] in benzene at room temperature resulting in the formation of several new pyrazoles **8a–j**, **13a–e**, **18a,b** isoxazoles **26a–g**, pyrazolo[3,4-*d*]pyridazines **9a–d** and isoxazolo[3,4-*d*]pyridazines **27a–d**.



Scheme 1

The double bond in compounds **2a–e** is electron rich and can thus undergo 1,3-dipolar cycloaddition reactions. Nitrilimines **4a,b**, [generated *in situ* by the action of triethylamine on *C*-acetyl-*N*-aryl hydrazonyl chlorides **3a,b**] have been reported to add to α,β-unsaturated carbonyl compounds to yield a mixture of isomeric pyrazolines.[19] Here the reaction of nitrilimines **4a,b** with enaminones **2a–e** in dry benzene at room temperature afforded only one isolable product in each case. These were assigned the pyrazole structure **8**. Compounds **8a–j** were assumed to be formed *via* a 1,3-dipolar cycloaddition of the nitrilimines **4a,b** to the activated double bond in compounds **2a–e** to afford the non-isolable intermediates **7a–j** which then lose dimethylamine yielding the pyrazole derivative **8**. Structure **6** was excluded on the basis of spectroscopic data of the isolated products (Scheme 2). It is of importance to report that compounds **9a–d** can not be prepared by the action of hydrazine on **6a–j** as shown in Scheme 2.

In the same manner, the enaminones **2a–e** reacted with *C*-(ethoxycarbonyl)-*N*-4-nitrophenylnitrilimine **11** liberated *in situ* from the hydrazonyl chloride **10** under the same reaction conditions to afford, in each case, a product that may be formulated as the pyrazole structure **12a–e** or its isomer **13a-e**. Structure **12** was excluded on the basis of



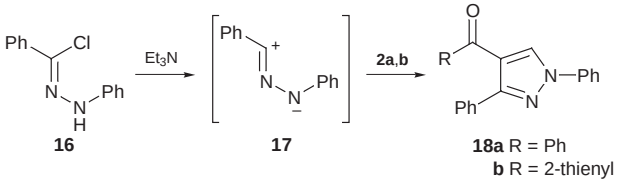
9	R	Ar
a	Ph	Ph
b	2-thienyl	Ph
c	2-pyridyl	Ph
d	Ph	C_6H_4Me-*p*

8	R	Ar
a	Ph	Ph
b	2-thienyl	Ph
c	2-furyl	Ph
d	2-pyrrolyl	Ph
e	2-pyridyl	Ph
f	Ph	C_6H_4Me-*p*
g	2-thienyl	C_6H_4Me-*p*
h	2-furyl	C_6H_4Me-*p*
i	2-pyrrolyl	C_6H_4Me-*p*
j	2-pyridyl	C_6H_4Me-*p*

Scheme 2

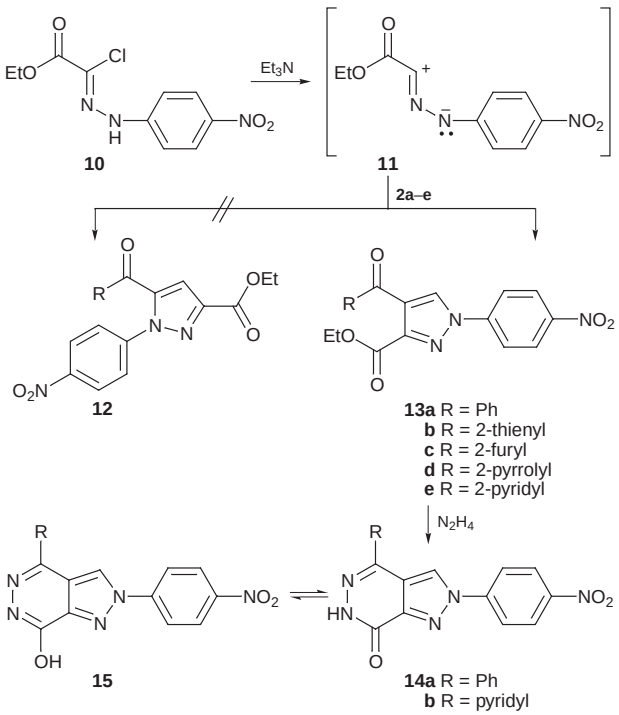
spectroscopic data (Scheme 3). Further confirmation of structure **13** comes from treating **13a,d** with hydrazine hydrate to afford the oxo form **14a,b**.

Treatment of **2a,b** with *C*-phenyl-*N*-phenylnitrilimine **17** afforded the pyrazole derivatives **18a,b** in good yields.

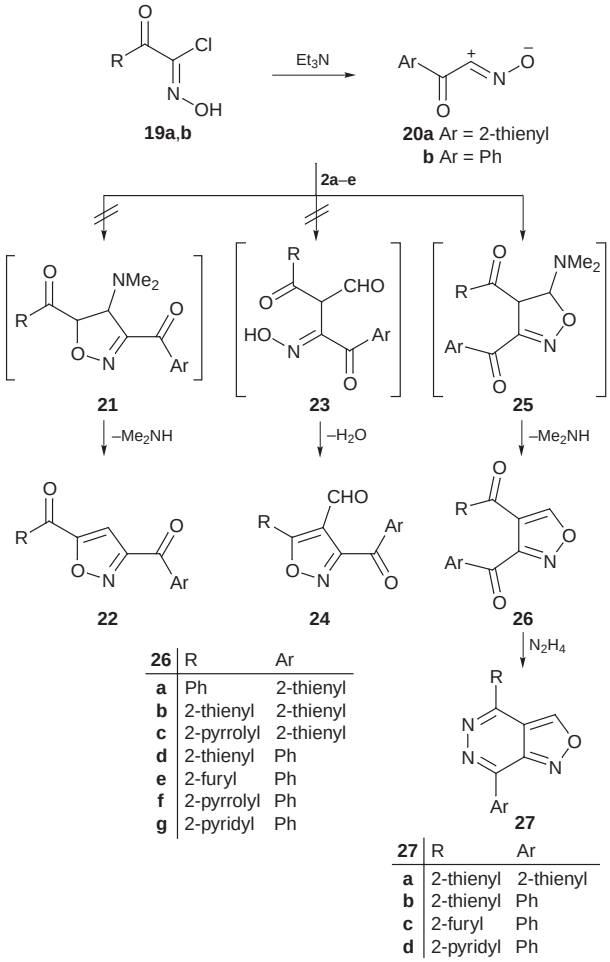


Prompted by these results, the reaction of enaminones **2a–e** with the nitrile oxides **20a,b** (generated *in situ* by the action of triethylamine on hydroximoyl chlorides **19a,b**) led to the formation of adducts which were converted into the isoxazole derivatives **22a–g** or the isomer **26a–g** *via*

* To receive any correspondence (*e-mail*: UVA3180@KAAU.edu.Sa).



Scheme 3



26	R	Ar
a	Ph	2-thienyl
b	2-thienyl	2-thienyl
c	2-pyrrolyl	2-thienyl
d	2-thienyl	Ph
e	2-furyl	Ph
f	2-pyrrolyl	Ph
g	2-pyridyl	Ph

27	R	Ar
a	2-thienyl	2-thienyl
b	2-thienyl	Ph
c	2-furyl	Ph
d	2-pyridyl	Ph

Scheme 4

elimination of dimethylamine from the non-isolable intermediate **21** or **25**, respectively, or into the isomer **24a–g** *via* loss of one water molecule from the non-isolable intermediate **23** (Scheme 4). Structure **22** was easily ruled out on the basis of spectroscopic data.

It is noteworthy to report that the enaminone **2e** reacted with nitrile oxide **20b**, in benzene at room temperature to afford a single product (TLC) with molecular formula $C_{16}H_{10}N_2O_3$. Structure **24g** or **26g** can be formulated for this reaction product on the basis of spectroscopic data. Structure **26g** was suggested on the basis of ^{13}C NMR data. A final confirmation of the latter structure was performed chemically by the action of hydrazine hydrate on **26g** to produce **27d**.

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Techniques used: IR, ^1H, ^{13}C NMR and mass spectrometry

References: 20

Schemes: 4

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